

University of Groningen

## Beyond risk-reducing salpingo-oophorectomy

Fakkert, Ingrid Elizabeth

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Fakkert, I. E. (2017). *Beyond risk-reducing salpingo-oophorectomy: On breast cancer risk and bone health*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

### Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

### Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



**Appendices**  
**References**  
**Dankwoord**  
**Curriculum vitae**

## References

1. Dutch Cancer Registry (IKNL). Dutch cancer figures. Available at: [www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl). Accessed July 15th, 2016.
2. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013; Available at: <http://globocan.iarc.fr>. Accessed July 15th, 2016.
3. Vos JR, Hsu L, Brohet RM, et al. Bias Correction Methods Explain Much of the Variation Seen in Breast Cancer Risks of BRCA1/2 Mutation Carriers. *J Clin Oncol* 2015; 33: 2553-2562.
4. van der Kolk DM, de Bock GH, Leegte BK, et al. Penetrance of breast cancer, ovarian cancer and contralateral breast cancer in BRCA1 and BRCA2 families: high cancer incidence at older age. *Breast Cancer Res Treat* 2010; 124: 643-651.
5. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; 72: 1117-1130.
6. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 2007; 25: 1329-1333.
7. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst* 2013; 105: 812-822.
8. Metcalfe K, Gershman S, Lynch HT, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2011; 104: 1384-1392.
9. Reding KW, Bernstein JL, Langholz BM, et al. Adjuvant systemic therapy for breast cancer in BRCA1/BRCA2 mutation carriers in a population-based study of risk of contralateral breast cancer. *Breast Cancer Res Treat* 2010; 123: 491-498.
10. Graeser MK, Engel C, Rhiem K, et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 2009; 27: 5887-5892.
11. van den Broek AJ, van 't Veer LJ, Hooning MJ, et al. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. *J Clin Oncol* 2016; 34: 409-418.
12. Molina-Montes E, Perez-Nevot B, Pollan M, Sanchez-Cantalejo E, Espin J, Sanchez MJ. Cumulative risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer: A systematic review and meta-analysis. *Breast* 2014; 23: 721-742.
13. Prat J. Pathology of cancers of the female genital tract. *Int J Gynaecol Obstet* 2015; 131 Suppl 2: S132-45.
14. Kurman RJ, Shih I. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *Am J Pathol* 2016; 186: 733-747.
15. Berek JS, Crum C, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 2015; 131 Suppl 2: S111-22.
16. Vencken PM, Reitsma W, Kriege M, et al. Outcome of BRCA1- compared with BRCA2-associated ovarian cancer: a nationwide study in the Netherlands. *Ann Oncol* 2013; 24: 2036-2042.
17. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* 2012; 307: 382-390.
18. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin Cancer Res* 2004; 10: 2473-2481.

19. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012; 30: 2654-2663.
20. Hennessy BT, Timms KM, Carey MS, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol* 2010; 28: 3570-3576.
21. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res* 2014; 20: 764-775.
22. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011; 474: 609-615.
23. Maistro S, Teixeira N, Encinas G, et al. Germline mutations in BRCA1 and BRCA2 in epithelial ovarian cancer patients in Brazil. *BMC Cancer* 2016; 16: 934.
24. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* 2001; 68: 700-710.
25. Commissie Richtlijnen Gynaecologische Oncologie. Epitheliaal ovariumcarcinoom, landelijke richtlijn, versie 2.0. 2012; Available at: <http://www.oncoline.nl/ovariumcarcinoom>. Accessed August 27th, 2017.
26. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. *Br J Cancer* 2006; 94: 814-819.
27. Hermesen BB, Olivier RI, Verheijen RH, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. *Br J Cancer* 2007; 96: 1335-1342.
28. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? *Int J Cancer* 2009; 124: 919-923.
29. Vasen HF, Tesfay E, Boonstra H, et al. Early detection of breast and ovarian cancer in families with BRCA mutations. *Eur J Cancer* 2005; 41: 549-554.
30. Evans DG, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. *J Med Genet* 2009; 46: 593-597.
31. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst* 2009; 101: 80-87.
32. Marchetti C, De Felice F, Palaia I, et al. Risk-reducing salpingo-oophorectomy: a meta-analysis on impact on ovarian cancer risk and all cause mortality in BRCA 1 and BRCA 2 mutation carriers. *BMC Womens Health* 2014; 14: 150-014-0150-5.
33. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002; 346: 1616-1622.
34. Finkelman BS, Rubinstein WS, Friedman S, et al. Breast and ovarian cancer risk and risk reduction in Jewish BRCA1/2 mutation carriers. *J Clin Oncol* 2012; 30: 1321-1328.
35. Kenkhuis MJ, de Bock GH, Elferink PO, et al. Short-term surgical outcome and safety of risk reducing salpingo-oophorectomy in BRCA1/2 mutation carriers. *Maturitas* 2010; 66: 310-314.
36. Commissie Richtlijnen Gynaecologische Oncologie. Erfelijk en familiair ovariumcarcinoom. Landelijke richtlijn, versie 1.0. 2015; Available at: [http://www.oncoline.nl/richtlijn/doc/index.php?type=pda&richtlijn\\_id=973](http://www.oncoline.nl/richtlijn/doc/index.php?type=pda&richtlijn_id=973). Accessed December 1st, 2016.

37. NABON (Nationaal borstkanker overleg Nederland). Breast cancer Dutch guideline Version 2.0. 2012; Available at: <http://oncoline.nl/uploaded/docs/mammacarcinoom/Dutch%20Breast%20Cancer%20Guideline%202012.pdf>. Accessed August 18th, 2013.
38. Groeneveld FP, Bareman FP, Barentsen R, Dokter HJ, Drogendijk AC, Hoes AW. The climacteric and well-being. *J Psychosom Obstet Gynaecol* 1993; 14: 127-143.
39. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992; 14: 103-115.
40. van Asperen CJ, Jonker MA, Jacobi CE, et al. Risk estimation for healthy women from breast cancer families: new insights and new strategies. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 87-93.
41. Antoniou AC, Easton DF. Risk prediction models for familial breast cancer. *Future Oncol* 2006; 2: 257-274.
42. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 1994; 73: 643-651.
43. Helder-Woolderink JM, Blok EA, Vasen HF, Hollema H, Mourits MJ, De Bock GH. Ovarian cancer in Lynch syndrome; a systematic review. *Eur J Cancer* 2016; 55: 65-73.
44. Burger HG. Androgen production in women. *Fertil Steril* 2002; 77 Suppl 4: S3-5.
45. Rosen MP, Cedars MI. Greenspan's Basic & Clinical Endocrinology, 9e Chapter 13. Female Reproductive Endocrinology and Infertility. New York, NY: The McGraw-Hill Companies; 2011.
46. Casper R. Clinical manifestations and diagnosis of menopause. 2016; Available at: [https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-menopause?source=see\\_link&sectionName=Menstrual%20cycle%20and%20endocrine%20changes&anchor=H171787387#H36](https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-menopause?source=see_link&sectionName=Menstrual%20cycle%20and%20endocrine%20changes&anchor=H171787387#H36). Accessed November 5th, 2016.
47. Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012; 97: 1159-1168.
48. Welt CK, McNicholl DJ, Taylor AE, Hall JE. Female reproductive aging is marked by decreased secretion of dimeric inhibin. *J Clin Endocrinol Metab* 1999; 84: 105-111.
49. Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 1996; 81: 1495-1501.
50. Finch CE. The menopause and aging, a comparative perspective. *J Steroid Biochem Mol Biol* 2014; 142: 132-141.
51. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocr Rev* 1998; 19: 397-428.
52. Reyes FI, Winter JS, Faiman C. Pituitary-ovarian relationships preceding the menopause. I. A cross-sectional study of serum follicle-stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone levels. *Am J Obstet Gynecol* 1977; 129: 557-564.
53. WHO Scientific Group. Research on the menopause in the 1990's. A report of the WHO Scientific Group. World Health Organization 1996; 866: 1-107.
54. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. *J Clin Endocrinol Metab* 2005; 90: 3847-3853.
55. Fogle RH, Stanczyk FZ, Zhang X, Paulson RJ. Ovarian androgen production in postmenopausal women. *J Clin Endocrinol Metab* 2007; 92: 3040-3043.

56. Nelson LR, Bulun SE. Estrogen production and action. *J Am Acad Dermatol* 2001; 45: S116-24.
57. Labrie F. All sex steroids are made intracellularly in peripheral tissues by the mechanisms of intracrinology after menopause. *J Steroid Biochem Mol Biol* 2015; 145: 133-138.
58. Korse CM, Bonfrer JM, van Beurden M, Verheijen RH, Rookus MA. Estradiol and testosterone levels are lower after oophorectomy than after natural menopause. *Tumour Biol* 2009; 30: 37-42.
59. Henderson VW. Gonadal hormones and cognitive aging: a midlife perspective. *Womens Health (Lond)* 2011; 7: 81-93.
60. Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. *Menopause Int* 2008; 14: 111-116.
61. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006; 7: 821-828.
62. Kagan R. Surgical menopause: still confused after all these years. *Menopause* 2012; 19: 491-493.
63. Orozco LJ, Tristan M, Vreugdenhil MM, Salazar A. Hysterectomy versus hysterectomy plus oophorectomy for premenopausal women. *Cochrane Database Syst Rev* 2014; 7: CD005638.
64. Pezaro C, James P, McKinley J, Shanahan M, Young MA, Mitchell G. The consequences of risk reducing salpingo-oophorectomy: the case for a coordinated approach to long-term follow up post surgical menopause. *Fam Cancer* 2012; 11: 403-410.
65. Clarke RB. Ovarian steroids and the human breast: regulation of stem cells and cell proliferation. *Maturitas* 2006; 54: 327-334.
66. Anderson E, Clarke RB. Steroid receptors and cell cycle in normal mammary epithelium. *J Mammary Gland Biol Neoplasia* 2004; 9: 3-13.
67. Howard BA, Gusterson BA. Human breast development. *J Mammary Gland Biol Neoplasia* 2000; 5: 119-137.
68. Macias H, Hinck L. Mammary gland development. *Wiley Interdiscip Rev Dev Biol* 2012; 1: 533-557.
69. Arendt LM, Kuperwasser C. Form and function: how estrogen and progesterone regulate the mammary epithelial hierarchy. *J Mammary Gland Biol Neoplasia* 2015; 20: 9-25.
70. Walker RA, Martin CV. The aged breast. *J Pathol* 2007; 211: 232-240.
71. Hickey TE, Robinson JL, Carroll JS, Tilley WD. Minireview: The androgen receptor in breast tissues: growth inhibitor, tumor suppressor, oncogene? *Mol Endocrinol* 2012; 26: 1252-1267.
72. Jacobsen BM, Horwitz KB. Progesterone receptors, their isoforms and progesterone regulated transcription. *Mol Cell Endocrinol* 2012; 357: 18-29.
73. Dahlman-Wright K, Cavaillès V, Fuqua SA, et al. International Union of Pharmacology. LXIV. Estrogen receptors. *Pharmacol Rev* 2006; 58: 773-781.
74. Curtis Hewitt S, Couse JF, Korach KS. Estrogen receptor transcription and transactivation: Estrogen receptor knockout mice: what their phenotypes reveal about mechanisms of estrogen action. *Breast Cancer Res* 2000; 2: 345-352.
75. Hilton HN, Graham JD, Clarke CL. Minireview: Progesterone Regulation of Proliferation in the Normal Human Breast and in Breast Cancer: A Tale of Two Scenarios? *Mol Endocrinol* 2015; 29: 1230-1242.
76. Schultz JR, Petz LN, Nardulli AM. Estrogen receptor alpha and Sp1 regulate progesterone receptor gene expression. *Mol Cell Endocrinol* 2003; 201: 165-175.

77. Hilton HN, Doan TB, Graham JD, et al. Acquired convergence of hormone signaling in breast cancer: ER and PR transition from functionally distinct in normal breast to predictors of metastatic disease. *Oncotarget* 2014; 5: 8651-8664.
78. Clarke RB, Howell A, Potten CS, Anderson E. Dissociation between steroid receptor expression and cell proliferation in the human breast. *Cancer Res* 1997; 57: 4987-4991.
79. Briskin C, Park S, Vass T, Lydon JP, O'Malley BW, Weinberg RA. A paracrine role for the epithelial progesterone receptor in mammary gland development. *Proc Natl Acad Sci U S A* 1998; 95: 5076-5081.
80. Russo J, Ao X, Grill C, Russo IH. Pattern of distribution of cells positive for estrogen receptor alpha and progesterone receptor in relation to proliferating cells in the mammary gland. *Breast Cancer Res Treat* 1999; 53: 217-227.
81. Carroll JS, Hickey TE, Tarulli GA, Williams M, Tilley WD. Deciphering the divergent roles of progestogens in breast cancer. *Nat Rev Cancer* 2017; 17: 54-64.
82. Quaynor SD, Stradtman EW, Jr, Kim HG, et al. Delayed puberty and estrogen resistance in a woman with estrogen receptor alpha variant. *N Engl J Med* 2013; 369: 164-171.
83. Navarrete MA, Maier CM, Falzoni R, et al. Assessment of the proliferative, apoptotic and cellular renovation indices of the human mammary epithelium during the follicular and luteal phases of the menstrual cycle. *Breast Cancer Res* 2005; 7: R306-13.
84. Soderqvist G, Isaksson E, von Schoultz B, Carlstrom K, Tani E, Skoog L. Proliferation of breast epithelial cells in healthy women during the menstrual cycle. *Am J Obstet Gynecol* 1997; 176: 123-128.
85. Key T, Appleby P, Barnes I, Reeves G, Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst* 2002; 94: 606-616.
86. Key TJ, Appleby PN, Reeves GK, et al. Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies. *Steroids* 2015; 99: 49-55.
87. Eliassen AH, Missmer SA, Tworoger SS, et al. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. *J Natl Cancer Inst* 2006; 98: 1406-1415.
88. Kaaks R, Tikk K, Sookthai D, et al. Premenopausal serum sex hormone levels in relation to breast cancer risk, overall and by hormone receptor status - results from the EPIC cohort. *Int J Cancer* 2014; 134: 1947-1957.
89. Schernhammer ES, Sperati F, Razavi P, et al. Endogenous sex steroids in premenopausal women and risk of breast cancer: the ORDET cohort. *Breast Cancer Res* 2013; 15: R46.
90. Fortner RT, Eliassen AH, Spiegelman D, Willett WC, Barbieri RL, Hankinson SE. Premenopausal endogenous steroid hormones and breast cancer risk: results from the Nurses' Health Study II. *Breast Cancer Res* 2013; 15: R19.
91. Dorgan JF, Stanczyk FZ, Kahle LL, Brinton LA. Prospective case-control study of premenopausal serum estradiol and testosterone levels and breast cancer risk. *Breast Cancer Res* 2010; 12: R98.
92. Kaaks R, Berrino F, Key T, et al. Serum sex steroids in premenopausal women and breast cancer risk within the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2005; 97: 755-765.
93. Thomas HV, Key TJ, Allen DS, et al. A prospective study of endogenous serum hormone concentrations and breast cancer risk in premenopausal women on the island of Guernsey. *Br J Cancer* 1997; 75: 1075-1079.



94. Rosenberg CR, Pasternack BS, Shore RE, Koenig KL, Toniolo PG. Premenopausal estradiol levels and the risk of breast cancer: a new method of controlling for day of the menstrual cycle. *Am J Epidemiol* 1994; 140: 518-525.
95. Micheli A, Muti P, Secreto G, et al. Endogenous sex hormones and subsequent breast cancer in premenopausal women. *Int J Cancer* 2004; 112: 312-318.
96. Missmer SA, Eliassen AH, Barbieri RL, Hankinson SE. Endogenous estrogen, androgen, and progesterone concentrations and breast cancer risk among postmenopausal women. *J Natl Cancer Inst* 2004; 96: 1856-1865.
97. McNamara KM, Moore NL, Hickey TE, Sasano H, Tilley WD. Complexities of androgen receptor signalling in breast cancer. *Endocr Relat Cancer* 2014; 21: T161-81.
98. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; 347: 1713-1727.
99. Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 1931-1943.
100. Marchbanks PA, Curtis KM, Mandel MG, et al. Oral contraceptive formulation and risk of breast cancer. *Contraception* 2012; 85: 342-350.
101. Beaber EF, Malone KE, Tang MT, et al. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. *Cancer Epidemiol Biomarkers Prev* 2014; 23: 755-764.
102. Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. *Cancer Res* 2014; 74: 4078-4089.
103. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. *Eur J Contracept Reprod Health Care* 2012; 17: 402-414.
104. Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-427.
105. Collins JA, Blake JM, Crosignani PG. Breast cancer risk with postmenopausal hormonal treatment. *Hum Reprod Update* 2005; 11: 545-560.
106. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013; 310: 1353-1368.
107. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. *Cochrane Database Syst Rev* 2017; 1: CD004143.
108. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701-1712.
109. Chlebowski RT, Barrington W, Aragaki AK, et al. Estrogen alone and health outcomes in black women by African ancestry: a secondary analyses of a randomized controlled trial. *Menopause* 2017; 24: 133-141.
110. Magnusson C, Baron JA, Correia N, Bergstrom R, Adami HO, Persson I. Breast-cancer risk following long-term oestrogen- and oestrogen-progestin-replacement therapy. *Int J Cancer* 1999; 81: 339-344.
111. Stahlberg C, Pedersen AT, Lynge E, et al. Increased risk of breast cancer following different regimens of hormone replacement therapy frequently used in Europe. *Int J Cancer* 2004; 109: 721-727.



112. Chen WY, Manson JE, Hankinson SE, et al. Unopposed estrogen therapy and the risk of invasive breast cancer. *Arch Intern Med* 2006; 166: 1027-1032.
113. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321-333.
114. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int J Cancer* 2005; 114: 448-454.
115. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003; 289: 3243-3253.
116. Yue W, Yager JD, Wang JP, Jupe ER, Santen RJ. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. *Steroids* 2013; 78: 161-170.
117. Simoes BM, Alferez DG, Howell SJ, Clarke RB. The role of steroid hormones in breast cancer stem cells. *Endocr Relat Cancer* 2015; 22: T177-86.
118. Chen W. Factors that modify breast cancer risk in women. 2016; Available at: <https://www.uptodate.com/contents/factors-that-modify-breast-cancer-risk-in-women?source=machineLearning&search=breast%20cancer%20estrogen&selectedTitle=4~150&sectionRank=1&anchor=H9#H1067591470>. Accessed November 19th, 2016.
119. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 2012; 13: 1141-1151.
120. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer* 2004; 111: 762-771.
121. Alsaker MD, Janszky I, Opdahl S, Vatten LJ, Romundstad PR. Weight change in adulthood and risk of postmenopausal breast cancer: the HUNT study of Norway. *Br J Cancer* 2013; 109: 1310-1317.
122. Ahn J, Schatzkin A, Lacey JV, Jr, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med* 2007; 167: 2091-2102.
123. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. *JAMA* 2006; 296: 193-201.
124. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control* 2002; 13: 741-751.
125. Feigelson HS, Jonas CR, Teras LR, Thun MJ, Calle EE. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 220-224.
126. Emaus MJ, van Gils CH, Bakker MF, et al. Weight change in middle adulthood and breast cancer risk in the EPIC-PANACEA study. *Int J Cancer* 2014; 135: 2887-2899.
127. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res* 2006; 8: R43.
128. Lambertini M, Santoro L, Del Mastro L, et al. Reproductive behaviors and risk of developing breast cancer according to tumor subtype: A systematic review and meta-analysis of epidemiological studies. *Cancer Treat Rev* 2016; 49: 65-76.

129. Meier-Abt F, Bentires-Alj M, Rochlitz C. Breast cancer prevention: lessons to be learned from mechanisms of early pregnancy-mediated breast cancer protection. *Cancer Res* 2015; 75: 803-807.
130. Russo IH, Russo J. Pregnancy-induced changes in breast cancer risk. *J Mammary Gland Biol Neoplasia* 2011; 16: 221-233.
131. Britt K, Ashworth A, Smalley M. Pregnancy and the risk of breast cancer. *Endocr Relat Cancer* 2007; 14: 907-933.
132. Meier-Abt F, Bentires-Alj M. How pregnancy at early age protects against breast cancer. *Trends Mol Med* 2014; 20: 143-153.
133. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet* 2002; 360: 187-195.
134. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; 387: 475-490.
135. Chowdhury R, Sinha B, Sankar MJ, et al. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. *Acta Paediatr* 2015; 104: 96-113.
136. Islami F, Liu Y, Jemal A, et al. Breastfeeding and breast cancer risk by receptor status--a systematic review and meta-analysis. *Ann Oncol* 2015; 26: 2398-2407.
137. Jernstrom H, Lubinski J, Lynch HT, et al. Breast-feeding and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2004; 96: 1094-1098.
138. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med* 2007; 356: 227-236.
139. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1159-1169.
140. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 2000; 92: 1081-1087.
141. Kelemen LE, Pankratz VS, Sellers TA, et al. Age-specific trends in mammographic density: the Minnesota Breast Cancer Family Study. *Am J Epidemiol* 2008; 167: 1027-1036.
142. Tamimi RM, Byrne C, Colditz GA, Hankinson SE. Endogenous hormone levels, mammographic density, and subsequent risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 2007; 99: 1178-1187.
143. Schoemaker MJ, Folkert EJ, Jones ME, et al. Combined effects of endogenous sex hormone levels and mammographic density on postmenopausal breast cancer risk: results from the Breakthrough Generations Study. *Br J Cancer* 2014; 110: 1898-1907.
144. Johansson H, Gandini S, Bonanni B, et al. Relationships between circulating hormone levels, mammographic percent density and breast cancer risk factors in postmenopausal women. *Breast Cancer Res Treat* 2008; 108: 57-67.
145. Varghese JS, Smith PL, Folkert E, et al. The heritability of mammographic breast density and circulating sex-hormone levels: two independent breast cancer risk factors. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 2167-2175.
146. Verheus M, Peeters PH, van Noord PA, van der Schouw YT, Grobbee DE, van Gils CH. No relationship between circulating levels of sex steroids and mammographic breast density: the Prospect-EPIC cohort. *Breast Cancer Res* 2007; 9: R53.

147. Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd Edition. *Breast Care (Basel)* 2013; 8: 149-154.
148. van der Groep P, van der Wall E, van Diest PJ. Pathology of hereditary breast cancer. *Cell Oncol (Dordr)* 2011; 34: 71-88.
149. Bertucci F, Finetti P, Birnbaum D. Basal breast cancer: a complex and deadly molecular subtype. *Curr Mol Med* 2012; 12: 96-110.
150. Palacios J, Robles-Frias MJ, Castilla MA, Lopez-Garcia MA, Benitez J. The molecular pathology of hereditary breast cancer. *Pathobiology* 2008; 75: 85-94.
151. Turner NC, Reis-Filho JS. Basal-like breast cancer and the BRCA1 phenotype. *Oncogene* 2006; 25: 5846-5853.
152. Mavaddat N, Barrowdale D, Andrulis IL, et al. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012; 21: 134-147.
153. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000; 406: 747-752.
154. Brekelmans CT, Tilanus-Linthorst MM, Seynaeve C, et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. *Eur J Cancer* 2007; 43: 867-876.
155. Bane AL, Beck JC, Bleiweiss I, et al. BRCA2 mutation-associated breast cancers exhibit a distinguishing phenotype based on morphology and molecular profiles from tissue microarrays. *Am J Surg Pathol* 2007; 31: 121-128.
156. Eerola H, Heikkilä P, Tamminen A, Aittomäki K, Blomqvist C, Nevanlinna H. Relationship of patients' age to histopathological features of breast tumours in BRCA1 and BRCA2 and mutation-negative breast cancer families. *Breast Cancer Res* 2005; 7: R465-9.
157. Visvader JE, Stingl J. Mammary stem cells and the differentiation hierarchy: current status and perspectives. *Genes Dev* 2014; 28: 1143-1158.
158. Buckley NE, Mullan PB. BRCA1--conductor of the breast stem cell orchestra: the role of BRCA1 in mammary gland development and identification of cell of origin of BRCA1 mutant breast cancer. *Stem Cell Rev* 2012; 8: 982-993.
159. Zonderland H, Wagner T, van Asperen C, et al. Kwaliteitsinstituut voor de Gezondheidszorg CBO, Richlijn mammacarcinoom 2008. 2008; Available at: [http://www.cbo.nl/Downloads/328/r1\\_mamma\\_o8.pdf](http://www.cbo.nl/Downloads/328/r1_mamma_o8.pdf). Accessed December 13th, 2011.
160. Kriege M, Brekelmans CT, Boetes C, et al. MRI screening for breast cancer in women with familial or genetic predisposition: design of the Dutch National Study (MRISC). *Fam Cancer* 2001; 1: 163-168.
161. Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA* 1996; 276: 33-38.
162. Brekelmans CT, Seynaeve C, Bartels CC, et al. Effectiveness of breast cancer surveillance in BRCA1/2 gene mutation carriers and women with high familial risk. *J Clin Oncol* 2001; 19: 924-930.
163. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004; 351: 427-437.
164. Rijnsburger AJ, Obdeijn IM, Kaas R, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol* 2010; 28: 5265-5273.

165. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. *Radiology* 2007; 242: 698-715.
166. Sardanelli F, Podo F, Santoro F, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. *Invest Radiol* 2011; 46: 94-105.
167. Warner E, Plewes DB, Shumak RS, et al. Comparison of breast magnetic resonance imaging, mammography, and ultrasound for surveillance of women at high risk for hereditary breast cancer. *J Clin Oncol* 2001; 19: 3524-3531.
168. Passaperuma K, Warner E, Causer PA, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. *Br J Cancer* 2012; 107: 24-30.
169. Lehman CD, Blume JD, Weatherall P, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer* 2005; 103: 1898-1905.
170. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 2004; 292: 1317-1325.
171. Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. Multimodality screening of high-risk women: a prospective cohort study. *J Clin Oncol* 2009; 27: 6124-6128.
172. Trecate G, Vergnaghi D, Manoukian S, et al. MRI in the early detection of breast cancer in women with high genetic risk. *Tumori* 2006; 92: 517-523.
173. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 2005; 23: 8469-8476.
174. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol* 2010; 28: 1450-1457.
175. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet* 2005; 365: 1769-1778.
176. Cortesi L, Turchetti D, Marchi I, et al. Breast cancer screening in women at increased risk according to different family histories: an update of the Modena Study Group experience. *BMC Cancer* 2006; 6: 210.
177. Hagen AI, Kvistad KA, Maehle L, et al. Sensitivity of MRI versus conventional screening in the diagnosis of BRCA-associated breast cancer in a national prospective series. *Breast* 2007; 16: 367-374.
178. Riedl CC, Ponhold L, Flory D, et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. *Clin Cancer Res* 2007; 13: 6144-6152.
179. Trop I, Lalonde L, Mayrand MH, David J, Larouche N, Provencher D. Multimodality breast cancer screening in women with a familial or genetic predisposition. *Curr Oncol* 2010; 17: 28-36.
180. Saadatmand S, Obdeijn IM, Rutgers EJ, et al. Survival benefit in women with BRCA1 mutation or familial risk in the MRI screening study (MRISC). *Int J Cancer* 2015; 137: 1729-1738.
181. Evans DG, Harkness EF, Howell A, et al. Intensive breast screening in BRCA2 mutation carriers is associated with reduced breast cancer specific and all cause mortality. *Hered Cancer Clin Pract* 2016; 14: 8.

182. Herrinton LJ, Barlow WE, Yu O, et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: a cancer research network project. *J Clin Oncol* 2005; 23: 4275-4286.
183. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2004; 22: 1055-1062.
184. Heemskerk-Gerritsen BA, Rookus MA, Aalfs CM, et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: a prospective analysis. *Int J Cancer* 2015; 136: 668-677.
185. Parazzini F, Braga C, La Vecchia C, Negri E, Acerboni S, Franceschi S. Hysterectomy, oophorectomy in premenopause, and risk of breast cancer. *Obstet Gynecol* 1997; 90: 453-456.
186. Robinson WR, Nichols HB, Tse CK, Olshan AF, Troester MA. Associations of Premenopausal Hysterectomy and Oophorectomy With Breast Cancer Among Black and White Women: The Carolina Breast Cancer Study, 1993-2001. *Am J Epidemiol* 2016; 184: 388-399.
187. Feinleib M. Breast cancer and artificial menopause: a cohort study. *J Natl Cancer Inst* 1968; 41: 315-329.
188. Arnold AG, Kauff ND. Prophylactic oophorectomy may differentially reduce breast cancer risk in women with BRCA1 versus BRCA2 mutations. *Current Breast Cancer Reports* 2009; 1: 157-161.
189. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. *J Clin Oncol* 2008; 26: 1331-1337.
190. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J Clin Oncol* 2005; 23: 7491-7496.
191. Chang-Claude J, Andrieu N, Rookus M, et al. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2007; 16: 740-746.
192. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA* 2010; 304: 967-975.
193. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. *J Natl Cancer Inst* 2015; 107: djv033.
194. Manolagas SC. Normal skeletal development and regulation of bone formation and resorption. 2016; Available at: [https://www.uptodate.com/contents/normal-skeletal-development-and-regulation-of-bone-formation-and-resorption?source=search\\_result&search=bone%20growth&selectedTitle=1~150](https://www.uptodate.com/contents/normal-skeletal-development-and-regulation-of-bone-formation-and-resorption?source=search_result&search=bone%20growth&selectedTitle=1~150). Accessed November 27th, 2016.
195. Almeida M, Laurent MR, Dubois V, et al. Estrogens and Androgens in Skeletal Physiology and Pathophysiology. *Physiol Rev* 2017; 97: 135-187.
196. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol* 2013; 9: 699-712.
197. Clarke BL, Khosla S. Female reproductive system and bone. *Arch Biochem Biophys* 2010; 503: 118-128.
198. Gordon CM, Zemel BS, Wren TA, et al. The Determinants of Peak Bone Mass. *J Pediatr* 2017; 180: 261-269.
199. Perry RJ, Farquharson C, Ahmed SF. The role of sex steroids in controlling pubertal growth. *Clin Endocrinol (Oxf)* 2008; 68: 4-15.

200. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab* 2007; 92: 2087-2099.
201. Looker AC, Wahner HW, Dunn WL, et al. Updated data on proximal femur bone mineral levels of US adults. *Osteoporos Int* 1998; 8: 468-489.
202. Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006; 367: 2010-2018.
203. Seifert-Klauss V, Schmidmayr M, Hobmaier E, Wimmer T. Progesterone and bone: a closer link than previously realized. *Climacteric* 2012; 15 Suppl 1: 26-31.
204. Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. *J Osteoporos* 2010; 2010: 845180.
205. Albright F, Smith PH, Richardson AM. Postmenopausal osteoporosis - its clinical features. *JAMA* 1941; 166: 2465.
206. RIVM. Volksgezondheidszorg.info: Aantal personen met osteoporose in de huisartspraktijk. 2016; Available at: <https://www.volksgezondheidszorg.info/onderwerp/osteoporose/cijfers-context/huidige-situatie#node-aantal-personen-met-osteoporose-de-huisartsenpraktijk>. Accessed April 4th, 2017.
207. Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ, 3rd. Trends in fracture incidence: a population-based study over 20 years. *J Bone Miner Res* 2014; 29: 581-589.
208. van Staa TP, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone* 2001; 29: 517-522.
209. Kuchuk NO, van Schoor NM, Pluijm SM, Smit JH, de Ronde W, Lips P. The association of sex hormone levels with quantitative ultrasound, bone mineral density, bone turnover and osteoporotic fractures in older men and women. *Clin Endocrinol (Oxf)* 2007; 67: 295-303.
210. Greendale GA, Edelstein S, Barrett-Connor E. Endogenous sex steroids and bone mineral density in older women and men: the Rancho Bernardo Study. *J Bone Miner Res* 1997; 12: 1833-1843.
211. Bjornerem A, Emaus N, Berntsen GK, et al. Circulating sex steroids, sex hormone-binding globulin, and longitudinal changes in forearm bone mineral density in postmenopausal women and men: the Tromso study. *Calcif Tissue Int* 2007; 81: 65-72.
212. Khosla S, Melton LJ, 3rd, Atkinson EJ, O'Fallon WM, Klee GG, Riggs BL. Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. *J Clin Endocrinol Metab* 1998; 83: 2266-2274.
213. Rariy CM, Ratcliffe SJ, Weinstein R, et al. Higher serum free testosterone concentration in older women is associated with greater bone mineral density, lean body mass, and total fat mass: the cardiovascular health study. *J Clin Endocrinol Metab* 2011; 96: 989-996.
214. Martins SL, Curtis KM, Glasier AF. Combined hormonal contraception and bone health: a systematic review. *Contraception* 2006; 73: 445-469.
215. Isley MM, Kaunitz AM. Update on hormonal contraception and bone density. *Rev Endocr Metab Disord* 2011; 12: 93-106.
216. Lopez LM, Chen M, Mullins Long S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. *Cochrane Database Syst Rev* 2015; 7: CD009849.
217. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA* 2003; 290: 1729-1738.

218. Banks E, Beral V, Reeves G, Balkwill A, Barnes I, Million Women Study Collaborators. Fracture incidence in relation to the pattern of use of hormone therapy in postmenopausal women. *JAMA* 2004; 291: 2212-2220.
219. Bagger YZ, Tanko LB, Alexandersen P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone* 2004; 34: 728-735.
220. Sioka C, Fotopoulos A, Georgiou A, Xourgia X, Papadopoulos A, Kalef-Ezra JA. Age at menarche, age at menopause and duration of fertility as risk factors for osteoporosis. *Climacteric* 2010; 13: 63-71.
221. Gerdhem P, Obrant KJ. Bone mineral density in old age: the influence of age at menarche and menopause. *J Bone Miner Metab* 2004; 22: 372-375.
222. Sullivan SD, Lehman A, Thomas F, et al. Effects of self-reported age at nonsurgical menopause on time to first fracture and bone mineral density in the Women's Health Initiative Observational Study. *Menopause* 2015; 22: 1035-1044.
223. Johansson H, Kanis JA, Oden A, et al. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res* 2014; 29: 223-233.
224. Wang Q, Huang Q, Zeng Y, et al. Parity and osteoporotic fracture risk in postmenopausal women: a dose-response meta-analysis of prospective studies. *Osteoporos Int* 2016; 27: 319-330.
225. Bjornerem A, Ahmed LA, Jorgensen L, Stormer J, Joakimsen RM. Breastfeeding protects against hip fracture in postmenopausal women: the Tromso study. *J Bone Miner Res* 2011; 26: 2843-2850.
226. WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ Tech Rep Ser* 1994; 843: 1-129.
227. CBO Kwaliteitsinstituut voor de gezondheidszorg, Nederlandse vereniging voor de reumatologie. Richtlijn osteoporose en fractuurpreventie, derde herziening. 2011; Available at: <http://www.diliguide.nl/document/1015/osteoporose-en-fractuurpreventie.html>. Accessed February 20th, 2014.
228. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312: 1254-1259.
229. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. *J Bone Miner Res* 2005; 20: 1185-1194.
230. Bagger YZ, Tanko LB, Alexandersen P, Hansen HB, Qin G, Christiansen C. The long-term predictive value of bone mineral density measurements for fracture risk is independent of the site of measurement and the age at diagnosis: results from the Prospective Epidemiological Risk Factors study. *Osteoporos Int* 2006; 17: 471-477.
231. Lewiecki EM, Gordon CM, Baim S, et al. International Society for Clinical Densitometry 2007 Adult and Pediatric Official Positions. *Bone* 2008; 43: 1115-1121.
232. Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. *Osteoporos Int* 2011; 22: 391-420.
233. Vasikaran S, Cooper C, Eastell R, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clin Chem Lab Med* 2011; 49: 1271-1274.
234. Michelsen TM, Dorum A, Dahl AA. A controlled study of mental distress and somatic complaints after risk-reducing salpingo-oophorectomy in women at risk for hereditary breast ovarian cancer. *Gynecol Oncol* 2009; 113: 128-133.



235. Challberg J, Ashcroft L, Lalloo F, et al. Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT. *Br J Cancer* 2011; 105: 22-27.
236. Cohen JV, Chiel L, Boghossian L, et al. Non-cancer endpoints in BRCA1/2 carriers after risk-reducing salpingo-oophorectomy. *Fam Cancer* 2012; 11: 69-75.
237. Bahar S, Abali R, Guzel S, et al. Comparison of the acute alterations in serum bone turnover markers and bone mineral density among women with surgical menopause. *Eur J Obstet Gynecol Reprod Biol* 2011; 159: 194-197.
238. Hashimoto K, Nozaki M, Inoue Y, Sano M, Nakano H. The chronological change of vertebral bone loss following oophorectomy using dual energy X-ray absorptiometry: the correlation with specific markers of bone metabolism. *Maturitas* 1995; 22: 185-191.
239. Peris P, Alvarez L, Monegal A, et al. Biochemical markers of bone turnover after surgical menopause and hormone replacement therapy. *Bone* 1999; 25: 349-353.
240. Yasumizu T, Fukada Y, Hoshi K. Changes in serum levels of type I collagen-related proteins after surgically induced menopause and correlations with bone loss in the lumbar spine. *Endocr J* 1999; 46: 337-343.
241. Ohta H, Makita K, Komukai S, Nozawa S. Bone resorption versus estrogen loss following oophorectomy and menopause. *Maturitas* 2002; 43: 27-33.
242. Morgante G, La Marca A, Ditto A, et al. Comparison of biochemical markers of bone turnover and bone mineral density in different groups of climacteric women. *Gynecol Endocrinol* 2001; 15: 466-471.
243. Garcia-Perez MA, Moreno-Mercer J, Tarin JJ, Cano A. Bone turnover markers and PTH levels in surgical versus natural menopause. *Calcif Tissue Int* 2004; 74: 143-149.
244. Heemskerk-Gerritsen BA, Brekelmans CT, Menke-Pluymers MB, et al. Prophylactic mastectomy in BRCA1/2 mutation carriers and women at risk of hereditary breast cancer: long-term experiences at the Rotterdam Family Cancer Clinic. *Ann Surg Oncol* 2007; 14: 3335-3344.
245. Rijnsburger AJ, Obdeijn IM, Kaas R, et al. BRCA1-associated breast cancers present differently from BRCA2-associated and familial cases: long-term follow-up of the Dutch MRISC Screening Study. *J Clin Oncol* 2010; 28: 5265-5273.
246. Meijers-Heijboer H, Brekelmans CT, Menke-Pluymers M, et al. Use of genetic testing and prophylactic mastectomy and oophorectomy in women with breast or ovarian cancer from families with a BRCA1 or BRCA2 mutation. *J Clin Oncol* 2003; 21: 1675-1681.
247. Metcalfe KA, Birenbaum-Carmeli D, Lubinski J, et al. International variation in rates of uptake of preventive options in BRCA1 and BRCA2 mutation carriers. *Int J Cancer* 2008; 122: 2017-2022.
248. National Institute of Clinical Excellence (NICE). National Institute of Clinical Excellence (NICE) guideline CG41 Familial Breast Cancer 2004 updated in 2006. 2006; Available at: <http://www.nice.org.uk/CG41>. Accessed February 17th, 2011.
249. Tardivon AA, Athanasiou A, Thibault F, El Khoury C. Breast imaging and reporting data system (BIRADS): magnetic resonance imaging. *Eur J Radiol* 2007; 61: 212-215.
250. Liberman L, Menell JH. Breast imaging reporting and data system (BI-RADS). *Radiol Clin North Am* 2002; 40: 409-30.
251. Obenauer S, Hermann KP, Grabbe E. Applications and literature review of the BI-RADS classification. *Eur Radiol* 2005; 15: 1027-1036.

252. Lowry R. Clinical calculator 1: from an observed sample - estimates of population prevalence, sensitivity, specificity, predictive values, and likelihood ratios. 2008; Available at: <http://faculty/vassar.edu/lowry/clin1.html>. Accessed February 17th, 2011.
253. Chiarelli AM, Majpruz V, Brown P, Theriault M, Shumak R, Mai V. The contribution of clinical breast examination to the accuracy of breast screening. *J Natl Cancer Inst* 2009; 101: 1236-1243.
254. Obdeijn IM, Loo CE, Rijnsburger AJ, et al. Assessment of false-negative cases of breast MR imaging in women with a familial or genetic predisposition. *Breast Cancer Res Treat* 2010; 119: 399-407.
255. Lu W, de Bock GH, Schaapveld M, Baas PC, Wiggers T, Jansen L. The value of routine physical examination in the follow up of women with a history of early breast cancer. *Eur J Cancer* 2011; 47: 676-682.
256. Sendag F, Cosan Terek M, Ozsener S, et al. Mammographic density changes during different postmenopausal hormone replacement therapies. *Fertil Steril* 2001; 76: 445-450.
257. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. *J Clin Oncol* 2005; 23: 8629-8635.
258. Shah P, Rosen M, Stopfer J, et al. Prospective study of breast MRI in BRCA1 and BRCA2 mutation carriers: effect of mutation status on cancer incidence. *Breast Cancer Res Treat* 2009; 118: 539-546.
259. Fakkert IE, Jansen L, Meijer K, et al. Breast cancer screening in BRCA1 and BRCA2 mutation carriers after risk reducing salpingo-oophorectomy. *Breast Cancer Res Treat* 2011; 129: 157-164.
260. Tilanus-Linthorst MM, Kriege M, Boetes C, et al. Hereditary breast cancer growth rates and its impact on screening policy. *Eur J Cancer* 2005; 41: 1610-1617.
261. Plevritis SK, Kurian AW, Sigal BM, et al. Cost-effectiveness of screening BRCA1/2 mutation carriers with breast magnetic resonance imaging. *JAMA* 2006; 295: 2374-2384.
262. Liberman L, Mason G, Morris EA, Dershaw DD. Does size matter? Positive predictive value of MRI-detected breast lesions as a function of lesion size. *AJR Am J Roentgenol* 2006; 186: 426-430.
263. Warner E, Hill K, Causer P, et al. Prospective study of breast cancer incidence in women with a BRCA1 or BRCA2 mutation under surveillance with and without magnetic resonance imaging. *J Clin Oncol* 2011; 29: 1664-1669.
264. Junod B, Zahl PH, Kaplan RM, Olsen J, Greenland S. An Investigation of the Apparent Breast Cancer Epidemic in France: Screening and incidence trends in birth cohorts. *BMC Cancer* 2011; 11: 401.
265. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol* 2005; 23: 7804-7810.
266. Eisen A, Lubinski J, Gronwald J, et al. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. *J Natl Cancer Inst* 2008; 100: 1361-1367.
267. Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst* 2008; 100: 475-482.
268. Kenemans P, Bundred NJ, Foidart JM, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol* 2009; 10: 135-146.

269. ACOG practice bulletin. Prophylactic oophorectomy. Number 7, September 1999 (replaces Technical Bulletin Number 111, December 1987). Clinical management guidelines for obstetrician-gynecologists. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1999; 67: 193-199.
270. Cragun JM. Screening for ovarian cancer. *Cancer Control* 2011; 18: 16-21.
271. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol* 2006; 7: 223-229.
272. Gallagher JC. Effect of early menopause on bone mineral density and fractures. *Menopause* 2007; 14: 567-571.
273. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocr Pract* 2016; 22: 1-42.
274. Compston J, Cooper A, Cooper C, et al. Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. 2014; Available at: [http://www.shef.ac.uk/NOGG/NOGG\\_Pocket\\_Guide\\_for\\_Healthcare\\_Professionals.pdf](http://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf). Accessed February 24th, 2017.
275. National Collaborating Centre for Cancer (UK). Osteoporosis: assessing the risk of fragility fracture. NICE clinical guideline 146. August 2012. 2017; Available at: <https://www.nice.org.uk/guidance/cg146>. Accessed February 24th, 2017.
276. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int* 2014; 25: 2359-2381.
277. National Institute of Health and Care Excellence (NICE). Familial breast cancer. NICE clinical guideline 164. June 2013. 2013; Available at: <https://www.nice.org.uk/guidance/cg164>. Accessed February 24th, 2017.
278. National Institute of Health and Care Excellence (NICE). Menopause: diagnosis and management. NICE Guideline 23. November 2015. 2015; Available at: <https://www.nice.org.uk/guidance/ng23>. Accessed February 24th, 2017.
279. Centre for Reviews and Dissemination editor. CRD's guidance for undertaking reviews in health care. Third ed. York, UK: York Publishing Services Ltd; 2009.
280. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; 62: 1006-1012.
281. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008-2012.
282. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 ed.: The Cochrane Collaboration; 2011.
283. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003; 7: iii-x, 1-173.
284. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; 52: 377-384.
285. Chittacharoen A, Theppisai U, Sirisriro R, Thanantaseth C. Pattern of bone loss in surgical menopause: a preliminary report. *J Med Assoc Thai* 1997; 80: 731-737.

286. Yasui T, Uemura H, Tomita J, et al. Change in serum undercarboxylated osteocalcin concentration in bilaterally oophorectomized women. *Maturitas* 2007; 56: 288-296.
287. Kritz-Silverstein D, Barrett-Connor E. Oophorectomy status and bone density in older, hysterectomized women. *Am J Prev Med* 1996; 12: 424-429.
288. Chittacharoen A, Theppisai U, Sirisriro R. Bone mineral density in natural and surgically-induced menopause. *Int J Gynaecol Obstet* 1999; 66: 193-194.
289. Hadjidakis D, Kokkinakis E, Sfakianakis M, Raptis SA. The type and time of menopause as decisive factors for bone mass changes. *Eur J Clin Invest* 1999; 29: 877-885.
290. Ohta H, Makita K, Komukai S, Nozawa S. Bone resorption versus estrogen loss following oophorectomy and menopause. *Maturitas* 2002; 43: 27-33.
291. Hadjidakis DJ, Kokkinakis EP, Sfakianakis ME, Raptis SA. Bone density patterns after normal and premature menopause. *Maturitas* 2003; 44: 279-286.
292. Hayirlioglu A, Gokaslan H, Andac N. The effect of bilateral oophorectomy on bone mineral density. *Rheumatol Int* 2006; 26: 1073-1077.
293. Kritz-Silverstein D, von Muhlen DG, Barrett-Connor E. Hysterectomy and oophorectomy are unrelated to bone loss in older women. *Maturitas* 2004; 47: 61-69.
294. Ozdemir S, Celik C, Gorkemli H, Kiyici A, Kaya B. Compared effects of surgical and natural menopause on climacteric symptoms, osteoporosis, and metabolic syndrome. *Int J Gynaecol Obstet* 2009; 106: 57-61.
295. Banks E, Reeves GK, Beral V, et al. Hip fracture incidence in relation to age, menopausal status, and age at menopause: prospective analysis. *PLoS Med* 2009; 6: e1000181.
296. Vesco KK, Marshall LM, Nelson HD, et al. Surgical menopause and nonvertebral fracture risk among older US women. *Menopause* 2012; 19: 510-516.
297. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009; 113: 1027-1037.
298. Jacoby VL, Grady D, Wactawski-Wende J, et al. Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. *Arch Intern Med* 2011; 171: 760-768.
299. Johansson C, Mellstrom D, Milsom I. Reproductive factors as predictors of bone density and fractures in women at the age of 70. *Maturitas* 1993; 17: 39-50.
300. Melton LJ,3rd, Crowson CS, Malkasian GD, O'Fallon WM. Fracture risk following bilateral oophorectomy. *J Clin Epidemiol* 1996; 49: 1111-1115.
301. Pansini F, Bagni B, Bonaccorsi G, et al. Oophorectomy and Spine Bone Density: Evidence of a Higher Rate of Bone Loss in Surgical Compared with Spontaneous Menopause. *Menopause* 1995; 2: 109-115.
302. Melton LJ,3rd, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. *J Bone Miner Res* 2003; 18: 900-905.
303. Centre for Metabolic Bone Diseases, University of Sheffield, UK. FRAX Fracture Risk Assessment Tool. 2016; Available at: <https://www.shef.ac.uk/FRAX/index.aspx>. Accessed February 24th, 2017.
304. Fletcher J. What is heterogeneity and is it important? *BMJ* 2007; 334: 94-96.
305. Seifert-Klauss V, Fillenbergs S, Schneider H, Lippa P, Mueller D, Kiechle M. Bone loss in premenopausal, perimenopausal and postmenopausal women: results of a prospective observational study over 9 years. *Climacteric* 2012; 15: 433-440.

306. Genant HK, Grampp S, Gluer CC, et al. Universal standardization for dual x-ray absorptiometry: patient and phantom cross-calibration results. *J Bone Miner Res* 1994; 9: 1503-1514.
307. Court-Brown CM, McQueen MM. Global Forum: Fractures in the Elderly. *J Bone Joint Surg Am* 2016; 98: e36.
308. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. *BIOG* 2005; 112: 956-962.
309. Luisetto G, Zangari M, Tizian L, et al. Influence of aging and menopause in determining vertebral and distal forearm bone loss in adult healthy women. *Bone Miner* 1993; 22: 9-25.
310. Kritz-Silverstein D, Barrett-Connor E. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women. *Am J Public Health* 1993; 83: 983-988.
311. Hreshchysyn MM, Hopkins A, Zylstra S, Anbar M. Effects of natural menopause, hysterectomy, and oophorectomy on lumbar spine and femoral neck bone densities. *Obstet Gynecol* 1988; 72: 631-638.
312. De Bock GH, Hesselink JW, Roorda C, et al. Model of care for women at increased risk of breast and ovarian cancer. *Maturitas* 2012; 71: 3-5.
313. Hospers IC, van der Laan JG, Zeebregts CJ, et al. Vertebral fracture assessment in supine position: comparison by using conventional semiquantitative radiography and visual radiography. *Radiology* 2009; 251: 822-828.
314. Hegeman JH, Willemsen G, van Nieuwpoort J, et al. Effective tracing of osteoporosis at a fracture and osteoporosis clinic in Groningen; an analysis of the first 100 patients. *Ned Tijdschr Geneesk* 2004; 148: 2180-2185.
315. Doorenbos CR, de Cuba MM, Vogt L, et al. Antiproteinuric treatment reduces urinary loss of vitamin D-binding protein but does not affect vitamin D status in patients with chronic kidney disease. *J Steroid Biochem Mol Biol* 2012; 128: 56-61.
316. Kelly TL. Bone Mineral Density reference databases for American men and women. *J Bone Min Res* 1990; 5: S249.
317. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8: 1137-1148.
318. Van der Lisdonk MW, van den Bosch WJHM, Lagro-Janssen ALM, Schers HJ editors. *Ziekten in de huisartspraktijk*. 5th ed. Maarssen: Elsevier gezondheidszorg; 2008.
319. Rubin DB. *Multiple imputation for non-response in surveys*. New York: Wiley; 1987.
320. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E. FRAX and its applications to clinical practice. *Bone* 2009; 44: 734-743.
321. Hippisley-Cox J, Coupland C. Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. *BMJ* 2012; 344: e3427.
322. Castelo-Branco C, Figueras F, Sanjuan A, Pons F, Vicente JJ, Vanrell JA. Long-term postmenopausal hormone replacement therapy effects on bone mass: differences between surgical and spontaneous patients. *Eur J Obstet Gynecol Reprod Biol* 1999; 83: 207-211.
323. Adams JE. Quantitative computed tomography. *Eur J Radiol* 2009; 71: 415-424.
324. Briot K, Paternotte S, Kolta S, et al. Added value of trabecular bone score to bone mineral density for prediction of osteoporotic fractures in postmenopausal women: the OPUS study. *Bone* 2013; 57: 232-236.

325. Sornay-Rendu E, Munoz F, Duboeuf F, Delmas PD. Rate of forearm bone loss is associated with an increased risk of fracture independently of bone mass in postmenopausal women: the OFELY study. *J Bone Miner Res* 2005; 20: 1929-1935.
326. Yildiz A, Sahin I, Gol K, Taner Z, Uluturk A, Biberoglu K. Bone loss rate in the lumbar spine: a comparison between natural and surgically induced menopause. *Int J Gynaecol Obstet* 1996; 55: 153-159.
327. Chapman JS, Powell CB, McLennan J, et al. Surveillance of survivors: follow-up after risk-reducing salpingo-oophorectomy in BRCA 1/2 mutation carriers. *Gynecol Oncol* 2011; 122: 339-343.
328. Fakkert IE, Abma EM, Westrik IG, et al. Bone mineral density and fractures after risk-reducing salpingo-oophorectomy in women at increased risk for breast and ovarian cancer. *Eur J Cancer* 2015; 51: 400-408.
329. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. *J Bone Miner Res* 2000; 15: 1526-1536.
330. Pacifici R, Brown C, Puscheck E, et al. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. *Proc Natl Acad Sci U S A* 1991; 88: 5134-5138.
331. Adami S, Bianchi G, Brandi ML, et al. Determinants of bone turnover markers in healthy premenopausal women. *Calcif Tissue Int* 2008; 82: 341-347.
332. Ardawi MS, Maimani AA, Bahksh TA, Rouzi AA, Qari MH, Raddadi RM. Reference intervals of biochemical bone turnover markers for Saudi Arabian women: a cross-sectional study. *Bone* 2010; 47: 804-814.
333. Sornay-Rendu E, Garnero P, Munoz F, Duboeuf F, Delmas PD. Effect of withdrawal of hormone replacement therapy on bone mass and bone turnover: the OFELY study. *Bone* 2003; 33: 159-166.
334. Hamwi A, Ganem AH, Grebe C, et al. Markers of bone turnover in postmenopausal women receiving hormone replacement therapy. *Clin Chem Lab Med* 2001; 39: 414-417.
335. Delmas PD, Davis SR, Hensen J, Adami S, van Os S, Nijland EA. Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. *Osteoporos Int* 2008; 19: 1153-1160.
336. Evans DG, Graham J, O'Connell S, Arnold S, Fitzsimmons D. Familial breast cancer: summary of updated NICE guidance. *BMJ* 2013; 346: f3829.
337. Eastell R, Hannon RA, Cuzick J, et al. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial (18233230). *J Bone Miner Res* 2006; 21: 1215-1223.
338. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. *Nat Rev Endocrinol* 2013; 9: 699-712.
339. Metcalfe K, Gershman S, Lynch HT, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer* 2011; 104: 1384-1392.
340. Metcalfe K, Lynch HT, Ghadirian P, et al. Risk of ipsilateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat* 2011; 127: 287-296.
341. Kotsopoulos J, Lubinski J, Lynch HT, et al. Oophorectomy after menopause and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1089-1096.
342. Basu NN, Ingham S, Hodson J, et al. Risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a 30-year semi-prospective analysis. *Fam Cancer* 2015; 14: 531-538.

343. Kotsopoulos J, Huzarski T, Gronwald J, et al. Bilateral Oophorectomy and Breast Cancer Risk in BRCA1 and BRCA2 Mutation Carriers. *J Natl Cancer Inst* 2017; 109: djw177.
344. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity, hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. *Breast Cancer Res* 2017; 19: 10.
345. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. *Biochim Biophys Acta* 2015; 1856: 73-85.
346. Sisti JS, Collins LC, Beck AH, Tamimi RM, Rosner BA, Eliassen AH. Reproductive risk factors in relation to molecular subtypes of breast cancer: Results from the nurses' health studies. *Int J Cancer* 2016; 138: 2346-2356.
347. Jones LP, Tilli MT, Assefnia S, et al. Activation of estrogen signaling pathways collaborates with loss of Brca1 to promote development of ERalpha-negative and ERalpha-positive mammary preneoplasia and cancer. *Oncogene* 2008; 27: 794-802.
348. Molyneux G, Smalley MJ. The cell of origin of BRCA1 mutation-associated breast cancer: a cautionary tale of gene expression profiling. *J Mammary Gland Biol Neoplasia* 2011; 16: 51-55.
349. Li W, Xiao C, Vonderhaar BK, Deng CX. A role of estrogen/ERalpha signaling in BRCA1-associated tissue-specific tumor formation. *Oncogene* 2007; 26: 7204-7212.
350. Hussein MR, Abd-Elwahed SR, Abdulwahed AR. Alterations of estrogen receptors, progesterone receptors and c-erbB2 oncogene protein expression in ductal carcinomas of the breast. *Cell Biol Int* 2008; 32: 698-707.
351. Liu C, Zhang H, Shuang C, et al. Alterations of ER, PR, HER-2/neu, and P53 protein expression in ductal breast carcinomas and clinical implications. *Med Oncol* 2010; 27: 747-752.
352. van Driel CM, Eltahir Y, de Vries J, et al. Risk-reducing mastectomy in BRCA1/2 mutation carriers: factors influencing uptake and timing. *Maturitas* 2014; 77: 180-184.
353. van Verschuer VM, Heemskerk-Gerritsen BA, van Deurzen CH, et al. Lower mitotic activity in BRCA1/2-associated primary breast cancers occurring after risk-reducing salpingo-oophorectomy. *Cancer Biol Ther* 2014; 15: 371-379.
354. Singh K, Lester J, Karlan B, Bresee C, Geva T, Gordon O. Impact of family history on choosing risk-reducing surgery among BRCA mutation carriers. *Am J Obstet Gynecol* 2013; 208: 329.e1-329.e6.
355. van der Aa JE, Hoogendam JP, Butter ES, Ausems MG, Verheijen RH, Zweemer RP. The effect of personal medical history and family history of cancer on the uptake of risk-reducing salpingo-oophorectomy. *Fam Cancer* 2015; 14: 539-544.
356. Kim D, Kang E, Hwang E, et al. Factors affecting the decision to undergo risk-reducing salpingo-oophorectomy among women with BRCA gene mutation. *Fam Cancer* 2013; 12: 621-628.
357. Siyam T, Ross S, Campbell S, Eurich DT, Yuksel N. The effect of hormone therapy on quality of life and breast cancer risk after risk-reducing salpingo-oophorectomy: a systematic review. *BMC Womens Health* 2017; 17: 22.
358. Roeke T, van Bommel AC, Gaillard-Hemmink MP, Hartgrink HH, Mesker WE, Tollenaar RA. The additional cancer yield of clinical breast examination in screening of women at hereditary increased risk of breast cancer: a systematic review. *Breast Cancer Res Treat* 2014; 147: 15-23.
359. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med* 2004; 351: 427-437.
360. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA* 2004; 292: 1317-1325.



361. Harmsen MG, Arts-de Jong M, Hoogerbrugge N, et al. Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study. *BMC Cancer* 2015; 15: 593.
362. Michelsen TM, Tonstad S, Pripp AH, Trope CG, Dorum A. Coronary heart disease risk profile in women who underwent salpingo-oophorectomy to prevent hereditary breast ovarian cancer. *Int J Gynecol Cancer* 2010; 20: 233-239.
363. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. *Maturitas* 2013; 75: 51-61.
364. Hibler EA, Kauderer J, Greene MH, Rodriguez GC, Alberts DS. Bone loss after oophorectomy among high-risk women: an NRG oncology/gynecologic oncology group study. *Menopause* 2016; 23: 1228-1232.
365. Garcia C, Lyon L, Littell RD, Powell B. Long-term outcomes in BRCA1/2 carriers who undergo risk-reducing salpingo-oophorectomy. *Gynecol Oncol* 2015; 137: 51.
366. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2011; 154: 356-364.
367. Callreus M, McGuigan F, Akesson K. Country-specific young adult dual-energy X-ray absorptiometry reference data are warranted for T-score calculations in women: data from the peak-25 cohort. *J Clin Densitom* 2014; 17: 129-135.
368. Dean-Colomb W, Hess KR, Young E, et al. Elevated serum P1NP predicts development of bone metastasis and survival in early-stage breast cancer. *Breast Cancer Res Treat* 2013; 137: 631-636.
369. Sullivan SD, Lehman A, Thomas F, et al. Effects of self-reported age at nonsurgical menopause on time to first fracture and bone mineral density in the Women's Health Initiative Observational Study. *Menopause* 2015; 22: 1035-1044.
370. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; 17: 1726-1733.



## Dankwoord

Eindelijk is het zover, mijn promotieonderzoek is afgerond! Ik heb dit proefschrift niet kunnen voltooien zonder de hulp van vele personen, van wie ik een aantal in het bijzonder wil bedanken.

Allereerst alle vrouwen die hebben deelgenomen aan de studies in dit proefschrift: bedankt voor deze bijdrage en voor het delen van persoonlijke ervaringen, waar ik in mijn werk als arts al veel aan heb gehad.

Mijn eerste promotor prof. dr. M.J.E. Mourits, beste Marian, ik bewonder de manier waarop jij onderzoek en patiëntenzorg combineert. Voor dit onderzoek hebben wij veel van jouw RRSO-patiëntes teruggezien, soms jaren later, maar jij kende iedereen, inclusief persoonlijk verhaal. Altijd hield jij de patiënte en haar behandelaar in jouw, en ook mijn, achterhoofd. Bedankt voor je kritische blik en inspiratie.

Mijn promotor prof. dr. G.H. de Bock, beste Truuske, jij bent mijn begeleider vanaf mijn allereerste onderzoeksproject. Van proefproject tot proefschrift heb jij mij onderwezen, begeleid en geïnspireerd in het doen van kwalitatief goed onderzoek, het combineren van werk en privé en het accepteren van beperkingen. Bedankt voor je visie en de tijd die je in mij geïnvesteerd hebt.

Mijn co-promotor dr. J.C. Oosterwijk, beste Jan, al vroeg was jij betrokken bij mijn proefschrift en heb jij mijn artikelen inhoudelijk en tekstueel naar een hoger plan getrokken. Veel later, tijdens mijn werk als ANIOS bij de klinische genetica hebben we ook in de patiëntenzorg veel samengewerkt. Bedankt dat ik altijd bij jou aan kon kloppen (eerst letterlijk, later figuurlijk) en voor de vele leermomenten in onderzoek en patiëntenzorg.

Mijn dank gaat uit naar de leden van de beoordelingscommissie, prof. dr. J.P. van den Bergh, prof. dr. ir. F.E. van Leeuwen en prof. dr. R.H. Sijmons voor het lezen en beoordelen van het manuscript van dit proefschrift.

Al mijn mede-auteurs hebben hun eigen onmisbare bijdrage geleverd aan de artikelen in dit proefschrift. Bedankt E.M. Abma, dr. M.J. Greuter, dr. L. Jansen, dr. T. Kok, dr. D.M. van der Kolk, dr. J.D. Lefrandt, dr. K. Meijer, prof. dr. R. Slart, dr. N. Teixeira, dr. E. van der Veer, dr. B van der Vegt, I.G. Westrik en prof. dr. B.H. Wolffenbuttel.

Lieve Elske-Marije, bedankt voor de samenwerking bij onze klinische studies, waarbij we samen het beleid bepaalden voor de vrouwen met RRSO die ik op de poli zag, voor jouw bijdrage aan onze systematische review, en bedankt dat je mij introduceerde tijdens IWO-meetings en osteoporosedagen. Samenwerken met jou was altijd leerzaam, gezellig, en zelfs voedzaam, met vele KeepCups echt lekkere koffie en bonbons.

Dear Natalia, we met when you started as a research student in the room on the other side of the hallway. Years later, you joined me in writing a review, and thanks to you, this review was finished and greatly improved. Next to a lot of writing, thinking and making long days in the office, we also had nice non-work-related conversations and I really enjoyed working with you. Thank you for your contributions to my PhD-thesis and congratulations on finishing your own!

Beste Eveline, bedankt voor alles wat je mij geleerd hebt over botombouw-parameters, jouw kritische blik op onze stukken en het feit dat ik altijd terecht kon voor vragen, zelfs na je pensionering.

Beste Iris, bedankt voor jouw voorwerk voor de botgezondheidstudies in het kader van jouw stage wetenschap. Bedankt ook dat je tijdens jouw werk in vele uithoeken van de wereld, altijd snel en belangstellend hebt gereageerd op onze manuscripten.

Daarnaast wil ik alle collega's op de poliklinieken Gynaecologie, Ouderengeneeskunde en Nucleaire Geneeskunde bedanken voor de ondersteuning bij het plannen en uitvoeren van poli- en DEXA-afspraken; evenals alle gynaecologen die tijdens hun reguliere spreekuur tijd hebben gemaakt voor de supervisie van mijn onderzoekspatiënten.

Ook wil de medewerkers op de secretariaten van de afdelingen gynaecologie en epidemiologie bedanken voor hun ondersteuning, in het bijzonder Heidi Buntjer, Janny Abels, Roelian Geuze, Petra Wetterauw en Aukje van der Zee.

Tijdens mijn promotietraject heb ik op meerdere werkplekken en afdelingen mogen werken, waardoor ik vele kamer- en ganggenoten heb gehad. Dus, met het risico iemand te vergeten (sorry!), Aniek, Renske, Meike, Irene, Catarina, Merel, Janna, Wise Guys Kim en Ineke, Maartje, Elsbeth, Marhin, Talita, Claudia, Florine, Kim, Marion, Violeta, Marloes, Marco en Janet, bedankt voor alle sparmomentjes en de broodnodige afleiding!

Een groot deel van dit proefschrift is tot stand gekomen tijdens parttime-dagen, terwijl ik ondertussen werkte als ANIOS bij de klinische genetica in het UMCG en later als onderzoeker bij het Radboudumc. Ik wil mijn voormalige collega's uit het UMCG (een leukere eerste baan had ik mij niet kunnen wensen!) en

huidige collega's uit het Radboudumc bedanken voor hun flexibiliteit, waardoor het voor mij haalbaar was om het werkende leven en een promotietraject te combineren. Daarnaast ook bedankt voor alle belangstelling, gezelligheid en ontzettend leerzame tijd.

Lieve vrienden en vriendinnen, familie en schoonfamilie, ondanks dat vele van mijn weekenden en avonden gevuld werden door promotieonderzoek. was er soms ook nog tijd voor leuke etentjes, borrels, uitjes en samen niets doen. Bedankt voor deze afleiding!

Rinke, Laura, Jeroen en Linda, wat fijn dat we elkaar al zo lang kennen en nog steeds zoveel leuke dingen samen doen! Helemaal nu ook wij naar het Zuiden geëmigreerd zijn, hoop ik dat daar nog veel spelletjesdagen en (verjaardags-) etentjes bij komen.

Lieve Erik, ook al lijken onze levenspaden en prioriteiten soms wat uiteen te lopen, het is altijd weer leuk om samen dingen te ondernemen. Bedankt voor jouw interesse en gezelligheid!

Slagroomsnoesjes, de tijd met jullie was tekenend voor mijn studententijd in Groningen. Hoewel we elkaar, nu iedereen over Nederland en Europa verspreid is geraakt, een stuk minder zien, blijft de tijd die wij samen doorbrengen als vanouds. Bedankt voor de vriendschap!

Lieve Hilly, Eric, Kinge, Inge, Richard, Jurjen, Roline, Laura, Marijn, Arthur en Joes, ik had nooit bedacht dat het hebben van schoonfamilie zo leuk kon zijn, ik heb waarschijnlijk veel geluk gehad. Bedankt voor jullie oneindige belangstelling, gezelligheid en het feit dat jullie altijd voor ons klaar staan!

Lieve ouders, Anton en Ria, zonder jullie zou ik nooit gekomen zijn waar ik nu ben. Bedankt voor jullie praktische en mentale steun, onbegrensd vertrouwen en altijd een fijne plek om thuis te komen! Rob en Heleen, ik vind het mooi om te zien hoe wij alle drie volstrekt andere kanten op gegaan zijn (verstandig van jullie) en hoe goed jullie terecht aan het komen zijn. Eda en Freek, wat fijn dat jullie al zo lang bij ons gezin horen, het is altijd leuk met z'n achten. Heleen, ik vind het hartstikke fijn dat jij mijn paranimf bent, maar nu eerst samen op vakantie!

Cézanne en Casanova, in mijn eerste jaar als promovendus zijn jullie bij mij komen wonen en sindsdien is thuiskomen elke dag een feestje, bedankt!

Lieve Stefan, van de elf jaar die wij nu samen zijn, hebben we een groot deel doorgebracht met promoveren, maar gelukkig ook met zoveel méér. Dank zij jouw hulp, ondersteuning en altijd pragmatische oplossingen heb ik dit proefschrift kunnen afronden en daarom is het niet meer dan logisch dat jij mijn paranimf bent. Bedankt voor alles en tot altijd!



## Curriculum Vitae

Ingrid Fakkert werd op 9 oktober 1988 geboren in Zwolle. In 2006 behaalde ze haar VWO diploma aan de Rijksscholengemeenschap Steenwijk. Ditzelfde jaar begon zij met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Tijdens haar Bachelor heeft zij succesvol het Bachelor Honours traject van de Junior Science Masterclass Groningen doorlopen. Tijdens dit Honours traject kwam zij voor het eerst in aanraking met de onderzoeksgroep van prof.dr. M.J.E. Mourits en prof. dr. G.H. de Bock, waar zij in 2008 startte met een proefproject. Daarna volgde bij dezelfde groep een stage Wetenschap die uitmondde in een eerste publicatie. In 2011 startte zij met een MD/PhD-traject onder leiding van prof. dr. M.J.E. Mourits, prof. dr. G.H. de Bock en dr. J.C. Oosterwijk, met als onderwerp de lange termijn gevolgen van de risico-reducerende salpingo-oophorectomie in vrouwen met een erfelijk verhoogd risico op mamma- en ovariumcarcinoom. Tijdens dit MD/PhD-traject combineerde zij coschappen in het Medisch Centrum Leeuwarden en het Universitair Medisch Centrum Groningen met het doen van onderzoek. In juli 2014 behaalde zij haar artsexamen en is zij gaan werken als arts-assistent niet in opleiding bij de afdeling klinische genetica van het Universitair Medisch Centrum Groningen. Sinds april 2016 werkt zij als wetenschappelijk onderzoeker bij prof. dr. N. Hoogerbrugge bij de afdeling humane genetica van het Radboudumc te Nijmegen, waar zij onderzoek doet naar het verbeteren van de herkenning van patiënten met erfelijke kanker. Zij woont samen met Stefan Wierda in Utrecht.







